Kidney Disease and Cognitive Impairment in Older Adults: The State of the Science

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ABSTRACT

The care of older adults can be greatly complicated when an individual is diagnosed with chronic kidney disease (CKD). CKD is a common disease with an estimated worldwide prevalence of 11% to 13%. Cognitive impairment is found in older adult patients with all stages of CKD, with a prevalence as high as 50%. The mechanisms leading to cognitive impairment in patients with CKD are conjectured to be related to a combination of vascular, hormonal, inflammatory, and CKD-related toxic factors that influence brain structure and function. Cognitive decline in older adults with CKD can lead to devastating complications for patients and their caregivers. There are no medications or treatments specified in clinical guidelines to prevent, delay, or treat cognitive impairment in patients with CKD. Researchers are beginning to explore the potential of exercise and increased physical activity to improve cognitive function in older adults with CKD. This review provides an overview of cognitive decline in older adults with CKD, the clinical implications, and current treatment options. *Journal of Clinical Exercise Physiology*. 2019;8(2):74–81.

Keywords: chronic kidney disease, cognition, physical activity, exercise

INTRODUCTION

Chronic kidney disease (CKD) is marked by the presence of structural or functional kidney damage that has been present for at least three months (1). Patients are evaluated for CKD through medical evaluation and assessment of laboratory values including serum creatinine and calculations of the estimated glomerular filtration rate (eGFR), to determine stages of CKD (1) (Table 1). The most commonly used eGFR equation is the CKD-EPI formula (1). CKD is a medical condition commonly experienced by older adults, particularly those over 60 years old (2). Impaired cognitive function has recently been identified as a likely consequence of CKD for older adults, although the etiology of this complication is less understood. Cognitive decline in CKD contributes to the high burden of symptoms experienced by older adults with CKD and leads to devastating consequences, including decreased health-related quality of life, an inability to adhere to medical regimens, and increased mortality rate (3,4). Cognitive impairment in older adults with CKD also has negative healthcare and societal implications, including increased cost of care (5). Therefore, it is critical for research to explore interventions, including exercise, to prevent, identify, treat, and slow the progression of cognitive impairment in older adults with CKD.

PREVALENCE

Cognitive impairment is evaluated through a variety of neuropsychological assessments and test batteries in clinical practice and research. The most commonly used test for initial patient evaluation is the Mini-Mental State Examination, which evaluates global cognition (4). Some recommend that patients with CKD be evaluated with tests of executive function (the ability to use metacognitive processing and coordination) since deficits in this domain have been noted in early

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TABLE 1. Stages of CKD.

Stage of CKD	eGFR
CKD Stage 1	≥ 90 mL•min^{-1}
CKD Stage 2	60 to 89 mL•min^{-1}
CKD Stage 3	30 to 59 mL•min^{-1}
CKD Stage 4	15 to 29 mL•min^{-1}
CKD Stage 5	< 15 mL•min^{-1}

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate per 1.73 m^{-2}

stages of CKD (4). In clinical practice, cognitive decline is often initially diagnosed as mild cognitive impairment, which is defined as accelerated cognitive decline beyond what is normally attributed to aging but not yet meeting criteria for dementia (6).

COGNITIVE IMPAIRMENT IN CHRONIC KIDNEY DISEASE

There is no cognitive function assessment test that is specifically designed for patients with CKD (4). The prevalence of cognitive impairment in patients with kidney disease is reported to be 13% to 50%, depending on the patient sample and method of cognitive assessment (7,8). Cognitive impairment is most apparent when kidney function declines to the extent that clearance of toxins is diminished, or when the eGFR is less than 60 mL·min^{-1}·1.73 m^{-2} (i.e., CKD Stage 3 of the 1 to 5 CKD severity scale noted in Table 1) (9). A decrease in eGFR is associated with a more rapid decline in cognitive function (3). Cognitive impairment is found in patients with CKD of all ages (10) but is particularly common in older adults (11). As many as 35% of adults over the age of 70 years have CKD in Stage 3 or 4 (2), which makes this population in great need of evaluation and interventions for cognitive impairment.

COGNITIVE IMPAIRMENT IN END STAGE RENAL DISEASE

When a patient's kidney function worsens to the extent that the kidneys can no longer maintain internal homeostasis (uremia develops requiring renal replacement therapy, such as hemodialysis (HD), peritoneal dialysis, or transplantation), a patient is diagnosed with end stage renal disease (ESRD) (1). The prevalence of cognitive impairment is estimated to be even higher in older adults with ESRD on HD, as compared to those with CKD (3). During HD a volume of the blood is removed from the patient's body and filtered through a semi-permeable membrane. This is postulated to potentially worsen cognitive function through hemodynamic instability affecting cerebral perfusion (7). In patients over the age of 70 years on HD, the prevalence of cognitive impairment in the executive function domain is reported to be as high as 60% (7). Moreover, in some samples of patients on HD, it has been reported that as few as 13% have normal cognitive function based on classification algorithms for mild cognitive impairment (7).

Cognitive impairment is not only seen in patients with ESRD requiring HD; it is also seen in patients on peritoneal dialysis, a procedure that utilizes the peritoneal membrane for fluid and solute exchange, during which less acute fluid and electrolyte shifts occur as compared to HD (12). The prevalence of cognitive impairment in patients on peritoneal dialysis is reported to be as high as 66% (12).

The exact prevalence of cognitive impairment in post kidney transplant recipients has not been thoroughly evaluated. In some studies, cognitive function has been noted to improve after kidney transplantation (13), whereas in other studies in older adult kidney transplant recipients, the 10-year incidence of dementia is between 5% and 17% (14). This high prevalence of cognitive impairment in patients after receiving a kidney transplant is concerning, since cognitive impairment has been related to an increased risk of transplanted organ (graft) loss and mortality for kidney transplant recipients (14).

PROPOSED PATHOPHYSIOLOGICAL MECHANISMS

Despite the high prevalence of cognitive impairment in patients with various kidney function issues, the exact cause of cognitive impairment in this population is not fully understood. The most commonly cited etiology of cognitive impairment in patients with non-dialysis dependent CKD is related to vascular dementia (3) through a complex interplay of physiological factors that influence brain function specifically related to vascular dysfunction, hormones, oxidative stress, inflammation, uremic toxins, and comorbid conditions including diabetes and hypertension (Figure 1). Several of these factors can be positively affected by exercise training in the general population and are potentially beneficial to cognitive function in the renal disease population (15,16).

Comorbidities

Hypertension and diabetes are the leading causes of CKD in the United States (17). In the general population, hypertension is associated with cognitive impairment from its effects on increasing the risk of vascular disease and stroke (18). In older adults in the general population, type 2 diabetes is also considered an independent risk factor for the development of cognitive impairment presumed to be caused by the vascular and metabolic risks and derangements associated with diabetes (19). Exercise improves hypertension in patients with CKD and ESRD (20), although it is unknown whether improvement in blood pressure in older adults with CKD is related to improved cognitive function. Anemia is common in older adults and associated with cognitive impairment in the older adult population (21). Anemia is hypothesized to be related to white matter disease, neuronal degeneration, micronutrient deficiencies, or as an indicator of overall health (21). In the general population, exercise can improve hemoglobin levels with a proposed mechanism of stimulating bone marrow production, which leads to increased red

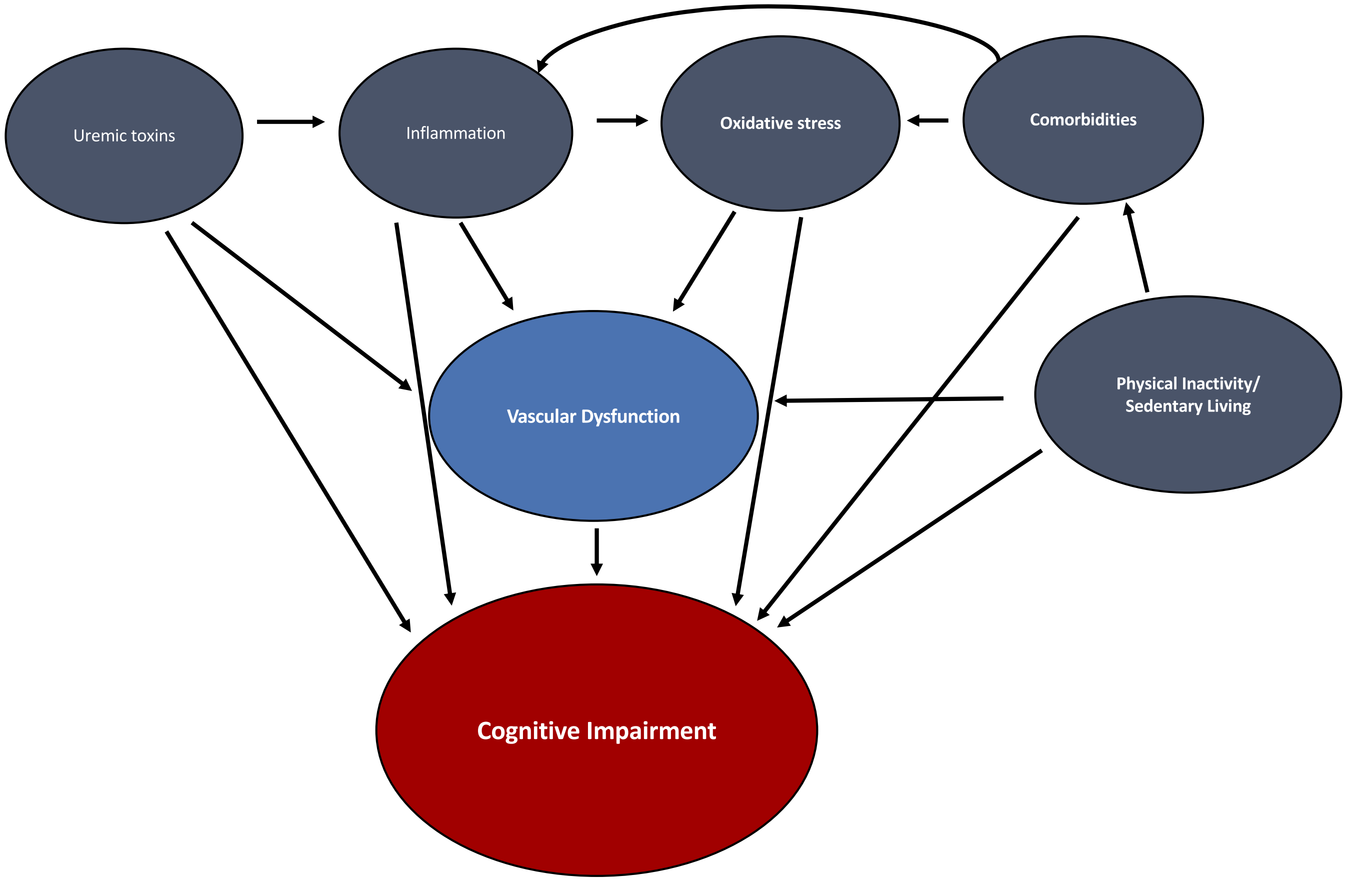

FIGURE 1. Proposed mechanisms of cognitive impairment in CKD.

blood cell production (22). However, in patients with CKD, anemia has less consistently been found to be associated with cognitive dysfunction, possibly due to methodological shortcomings in studies that have evaluated this relationship and due to the potential of other confounding factors that lead to the development of anemia (23).

Toxins, Uremic Molecules, and Oxidative Stress

By definition, patients with CKD have abnormal levels of circulating uremic toxins and mediators of oxidative stress (24). When a patient has CKD, the kidneys are unable to fully clear the byproducts of protein metabolism, and uremic toxins accumulate in the bloodstream (24). Although associations have been found between cognitive impairment and certain uremic toxins, the exact mechanism by which these toxins cause cognitive impairment is less understood (24). Toxins and uremic molecules are believed to influence brain function and contribute to the vascular dysfunction of CKD (20,25). Uremic toxins may also have a direct neurotoxic effect on the brain (26) and are believed to contribute to decreased vascular compliance by promoting ossification of vascular smooth muscle cells, causing arterial stiffness, and endothelial dysfunction (25). Arterial stiffness is associated with worse cognitive performance on a variety of cognitive tests in the general population (27). These results are similarly found in patients receiving HD, where arterial stiffness was a predictor of cognitive impairment (28). Arterial stiffness decreases as a result of exercise training in adults in the general population and as well in adults with ESRD receiving HD (29,30). It is hypothesized that exercise stimulates the release of nitric oxide, leading to improvement in vasodilation and reduced arterial stiffness (20).

Oxidative stress is also implicated in the cognitive impairment of patients with CKD. Oxidative stress is the imbalance between the production of pro-oxidants and the activity of antioxidants in the body (25). Patients with CKD have increased oxidative stress from circulating uremic toxins (25). Oxidative stress is believed to promote calcification of vascular smooth muscle cells and contribute to endothelial dysfunction by promoting the breakdown of nitric oxide, thereby disrupting vascular homeostasis (20,25). It is unclear if oxidative stress contributes to cognitive impairment through vascular mechanisms or if oxidative stress directly affects the brain. In the general population, the presence of biomarkers of oxidative damage in the cerebrospinal fluid is linked to mild cognitive impairment (31). Exercise training improves markers of oxidative damage in the general population (31). Exercise causes increased antioxidant production, which is the proposed mechanism that leads to decreased oxidative stress (18).

In patients with CKD, uremic toxins and oxidative stress are believed to have a key role in the development of vascular disease, which is implicated as a major cause of their cognitive impairment. Based on presentation and risk factors, patients with CKD are commonly found to have vascular cognitive impairment, a syndrome defined by the presence of a cognitive disorder and history or imaging that suggests a link between vascular disease and cognitive impairment (33). In patients with CKD, structural changes in the brain have been identified on MRI that are suggestive of microvascular changes and associated hypoperfusion (34). The kidney and brain are both low resistance organs that are passively perfused. These similarities have led to the hypothesis that the vascular disease causing end organ damage in the kidney in patients with CKD is also occurring in the brain and contributing to cognitive impairment (35).

Older adults with CKD are at further risk for decreased vascular compliance because of physical inactivity. Most patients with CKD do not meet the recommended daily volume of physical activity, particularly older adults (36). Physical inactivity in older adults in the general population is associated with cognitive impairment and cognitive decline, as compared to those who were physically active (36,37). This association needs further exploration in older adults with CKD.

Inflammation

Inflammation is implicated in the cognitive impairment found in patients with CKD. Patients with CKD are in a pro-inflammatory state from oxidative stress caused by uremic toxins (25). Inflammation is hypothesized to affect brain plasticity and hippocampal neural function, both of which could contribute to cognitive impairment (38). Inflammatory cytokines contribute to vascular calcification in patients with CKD, which appears to have a role in brain structural changes and cognitive impairment (25). Markers of inflammation in adults with CKD have been found to improve with exercise training, including increased IL-10 after a single bout of exercise and reduction in the ratio of IL-6 to IL-10 with regular exercise (walking) training (32). The exact mechanism by which exercise lowers these levels is unclear, but it is proposed that downregulation of T-lymphocyte and monocyte activation may play a role (32).

Alzheimer's Disease

Alzheimer's disease is also related to cognitive impairment in patients with CKD. CKD and Alzheimer's disease share similar risk factors, including hypertension, atherosclerosis, diabetes, cardiac disease, elevated homocysteine levels, and microvascular disease (39). Although there is a potential relationship between vascular dysfunction and Alzheimer's disease, the prevalence of Alzheimer's disease in patients with CKD is similar to the prevalence of Alzheimer's disease in patients without CKD (40). Therefore, it is unclear if Alzheimer's disease is a consequence of CKD or a comorbidity experienced by patients with CKD due to similar risk factors between the two diseases.

CEREBRAL CHANGES

The culmination of these insults may lead to changes in brain structure and function that are associated with cognitive impairment in patients with CKD. Comorbid conditions, exposure to uremic toxins, and vascular dysfunction can result in microvascular changes and hypoperfusion of brain tissue, potentially leading to the white matter changes noted on MRI (34). White matter changes and lesions are considered markers of cerebral small vessel disease (34). In the general population, cognitive impairment is associated with white matter microstructural changes (41). Decreased kidney function is associated with the volume of the white matter, as well as white matter lesions and lacunar infarcts (34). When white matter lesions are found in patients with CKD, performance on cognitive function tests are lower than in patients with CKD without white matter lesions (42). These radiological changes suggest that factors leading to vascular disease and brain hypoperfusion have a role in the cognitive impairment of patients with CKD.

CLINICAL IMPLICATIONS

The care of older adults with CKD is complex, and requires healthcare providers to assess, evaluate, and manage numerous comorbidities and complications of CKD. The care of patients with CKD includes assessment and management of hypertension, hyperlipidemia, bone mineralization disorders, anemia, protein-energy malnutrition, and electrolyte disorders (1). Cognitive impairment further complicates this already intricate management plan for patients with CKD and their caregivers.

Cognitive impairment is associated with functional decline leading to loss of independence and decreased quality of life in patients with CKD (3,4). Patients with CKD and cognitive impairment may have a limited decision-making capacity and ability to comply with medical treatments (3). This is particularly concerning since self-management, self-care, and participation in medical decision making is essential for patients with CKD to adhere to their complex care regimen (4,35). These patients often have a caregiver who assists with their care (35). When patients with CKD have cognitive impairment there can also be great stress and burden on the patient's social support network and caregivers (43). It is critically important that cognitive impairment in older adults with CKD is identified and addressed to prevent significant consequences from occurring.

RELIEVING FACTORS

Unfortunately, there is no medical treatment that is specified in clinical guidelines to prevent, delay, or treat cognitive impairment in patients with CKD. Although there are medications to treat Alzheimer's disease and dementia, there are no medications with the indication to treat vascular dementia or the cognitive impairment seen in patients with CKD (17). Additionally, there has not been an evaluation of the safety or efficacy of medications to treat Alzheimer's disease in patients with CKD (35). In studies of patients on HD, treatment of anemia with erythropoietin is associated with improved cognitive function, but these studies lacked rigor, and excessive erythropoietin administration is known to have significant cardiovascular risks (35).

The treatment of vascular risk factors and improving the uremic environment show promise in improving cognitive function for patients with CKD. Kidney transplantation resolves uremia and improves cognitive impairment (13), but unfortunately, there is still a high prevalence of cognitive impairment in patients who have received kidney transplants (14). Treatment of hypertension reduces the risk of cognitive impairment in older adults in the general population, but this was not statistically significant (44). The influence of intensive hypertension management on cognitive function in older adults with CKD has not been fully investigated.

LIFESTYLE INTERVENTIONS

Lifestyle interventions, particularly exercise and increased physical activity, have the potential to improve cognitive impairment in older adults with CKD. In the general population, physical activity, even at low-to-moderate levels, protects against cognitive decline in patients without dementia (45). Physical activity is related to increased blood flow and oxygen delivery to the brain, reduced cardiovascular risk factors, decreased cortisol levels, and neurotrophic effects on the brain (45). In the general population, these benefits of physical activity are believed to protect against cognitive impairment. Exercise is associated with increased volume of the hippocampus and decreased cerebral atrophy, which is proposed to be the result of increased brain angiogenesis, neurogenesis, and synaptogenesis (46,47). The role of exercise in improving cognition has not been consistent across all intervention studies with some finding improvements in cognition after exercise (16,46,48–59), whereas others have noted no improvement (60–63).

The potential role of increased physical activity or exercise training for improving cognitive function in patients with kidney disease is being explored. In patients receiving HD, those with higher levels of physical activity have better cognitive function (64). Improvements are also noted in cognition after exercise interventions, with improved cognizance being found on the Mini-Mental State Examination after a six-month intervention of strengthening and stretching for patients on HD (65). It is unclear if this association is related to the benefits of increased physical activity as noted in the general population or whether increased physical activity influences a unique aspect of the pathophysiology of cognitive impairment in kidney disease. Exercise training improves vascular function in patients with CKD (20), but it is not established if these improvements lead to changes in brain microvasculature or cognitive function. Further research is needed to explore the potential for lifestyle interventions to improve cognitive function in patients with CKD.

Although there is limited data on the effects of exercise and physical activity on cognitive function in older adults with CKD, increasing physical activity and exercise is recommended for individuals with CKD to promote health and reduce cardiac risk. It is recommended that patients with ESRD on HD exercise 30 min on most days of the week, per the National Kidney Foundation KDOQI Guidelines (66). The recommendation is similar for patients with CKD. The American College of Sports Medicine (ACSM) and the American Heart Association (AHA) recommend that people with chronic diseases exercise at moderate intensity for at least 30 min (or vigorous exercise for 20 min), five or more days per week to reduce cardiovascular risk (67,68)

TABLE 2. Exercise recommendations for patients with CKD.

Frequency	Most Days of the Week
Intensity	Moderate intensity May be guided by ratings of perceived exertion or heart rate reserve.
Time	May be individualized depending on functional status. • At least three times per week: A minimum of accumulated 30 to 45 min. • For cognitive improvement at least 45 min. Can be shorter than 10-min bouts accumulating to desired daily total.
Type	Multi-component exercise consisting of: • Large muscle aerobic • Low intensity-moderate strength • Balance exercises • Include a warm-up and cool-down period

Developed from 2018 Physical Activity Guidelines (16), the ACSM and ACSM/AHA Guidelines (67,68), and Johansen (69).

There are numerous difficulties and complexities when prescribing exercise for older adults with CKD and cognitive impairment. Cognitive impairment in older adults with CKD makes it more difficult for patients to adhere to medical recommendations (3,4). Older adults with CKD also have a large burden of other comorbidities, which need to be considered when prescribing an exercise regimen. Timing, intensity, and type of exercise need to be addressed while considering the unique needs of those with other co-morbidities.

Although there is more research needed on exercise interventions for older adults with CKD not yet on dialysis, there are some recommendations for an exercise prescription in this population (69) (Table 2). In her paper, Johansen recommended that patients with CKD be regularly evaluated by a healthcare provider about their current level of exercise and physical activity participation (69). Patients with CKD should be screened for symptoms of cardiac disease prior to a healthcare provider recommending initiation of an exercise program (69). The type of exercise that is ideal for patients with CKD is less clear, and more research is needed. Large muscle aerobic activities of moderate intensity done three or more times per week appear appropriate and have been recommended for patients with CKD (69). Additionally, if a patient reports weakness, strength training of low intensity could be suggested (69). However, in our opinion strength training could be started earlier than after subjective complaints of weakness. Exercise prescriptions should include a warm-up and cool-down and be individually tailored according to a rating of perceived scale of exertion to promote adherence (69). People with chronic diseases should exercise at a moderate intensity (i.e., brisk walking) for at least 30 min (or vigorous exercise (i.e., jogging) for 20 min), five or more days per week (67,68). Additionally, older adults that are at risk for falls should perform exercises to support balance (67). The current guidelines from ACSM/AHA, although not specifically designed for patients with CKD, provide an initial framework for prescribing therapeutic exercise to patients with CKD (67,68). Further research is needed to form the ideal exercise prescription recommendations specifically for older adults with CKD. And finally, a prudent suggestion is that exercise training be stopped and a referral made to the patient's physician (or contact physician for recommendation) if the hematocrit drops below 7% or the hemoglobin level is less than 8 gm·dL^{-1} (68).

KEY TAKEAWAYS FOR THE CLINICAL EXERCISE PHYSIOLOGIST

- Cognitive impairment is common in older adults with kidney disease.
- Cognitive impairment in patients with CKD is related to a complex interplay of factors that influence vascular function and brain function.
- Cognitive impairment in CKD adds increased complexity to the already intricate plan of care of older adults with CKD.
- Exercise and increased physical activity have the potential to improve cognitive impairments in older adults with CKD.
- Exercise and increasing physical activity are recommended for individuals with CKD.
- The exercise prescription for older adults with CKD should consider patient comorbidities, including cardiovascular disease, cognitive function, and current level of physical function.
- Large muscle aerobic activities, strength training, and balance exercises are recommended for all patients with chronic diseases, including those with CKD.
- Multicomponent, moderate-intensity exercise training performed three or more times per week, for a duration of 30 min to 45 min per session, is recommended.

CONCLUSION

CKD is a common disease that leads to a multitude of symptoms and comorbidities for older adults. Cognitive impairment is especially prevalent in older adults with CKD, and the level of kidney dysfunction is associated with the degree of cognitive impairment. The exact cause of cognitive impairment in patients with CKD remains to be fully elucidated, although it appears to be related to a complex interplay of pathophysiological processes. Cognitive impairment in this at-risk population has potentially serious consequences for patients and those that care for them. Lifestyle interventions, specifically increased physical activity and exercise, have the potential to improve cognitive impairment, but additional research and exploration is needed.

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